REMARKS

Claims

Claims 1-3, 8-13 and 22 are currently under examination pursuant to the restriction requirement mailed February 22, 2008.

Claims 17-18 are withdrawn from consideration as per the aforementioned restriction/election requirement.

Claims 4-8, 14–16 and 19–21 are hereby cancelled without prejudice or disclaimer.

Claims 23 and 24 are added by this paper.

Claim amendments

New claims 23 and 24 are supported, at least, by the disclosure contained in Examples 2 and 3 of the original specification. No new matter is added. Entry thereof is earnestly solicited.

Rejections under 35 U.S.C. §112, ¶1

Claims 1–3, 8–13 and 22 are rejected under this section as allegedly lacking enablement. The enablement rejection under this section is directed to method(s) for obtaining the claimed crystals. The Examiner alleges that crystallization of proteins is complex and the instant specification does not provide an enabling disclosure on crystallization of antibodies other than Erbitux®. The Office Action has applied new references to reject the claims under §112, ¶1 as allegedly lacking enablement. According to the Examiner, these new references generically establish that antibody crystallization is unpredictable and the specification does not provide enablement for making the claimed antibody crystals using *any* preparative method(s) other than what is immediately exemplified in Examples 2 and 3. See the paragraphs spanning pages 4-10 of the Office Action. These contentions are respectfully traversed.

In the paragraphs bridging pages 5 and 7 of the Office Action, the Examiner alleges that based on the decision rendered in ***In re Wands*** 8 USPQ2d 1400 (CAFC 1988), i.e., *Wands factors*, the scope of the claimed subject matter does not satisfy the statutory requirements under §112, ¶1. The Examiner asserts that these are the factors are to be considered when determining whether a disclosure satisfies the enablement requirement under 35 U.S.C. §112, ¶1. However, this is not an accurate description of the analysis of the *Wands* factors.

The Wands factors are to be used for determining whether undue experimentation is required for enablement. As expressly stated by the court in ***In re Wands***, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988), "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, ..." However, before the issue of undue experimentation arises, the rejection first must present reasons to doubt the veracity of the enablement statements presented in the specification.

Nature of the invention and breadth of the claims

The claimed invention refers to a crystal of an anti-epidermal growth factor receptor (anti-EGFR) antibody which is chimeric monoclonal antibody c225 (cetuximab) which forms a biologically active antibody protein when dissolved or suspended in an aqueous medium, wherein the crystal is obtained by precipitating an aqueous solution or suspension of the anti-EGFR antibody by means of a precipitation reagent. See claim 1. Claims 2, 3, along with newly added claims 23 and 24 recite the types of precipitation reagents used in making the crystals, e.g., a salt, a polymer, an organic solvent, or a combination thereof which is, for example, ammonium sulfate, sodium acetate, sodium citrate, potassium phosphate, PEG and/or ethanol. Further claimed herein are medicaments and/or pharmaceutical preparations comprising the crystals of the instant invention and another agent, e.g., a stabilizing agent or a pharmaceutically acceptable carrier. Another aspect of Applicants' claimed invention is directed to the process of making the crystals of the instant application, comprising, precipitating an aqueous solution or suspension of anti-EGFR chimeric monoclonal antibody c225 (cetuximab) by means of a precipitation reagent, and separating the precipitation product. See claim 9. Dependent claims 10 and 11 recite further aspects of the precipitating reagent. The present specification provides an enabling disclosure for making and using the claimed crystals and/or preparations thereof in a manner recited in the claims.

In levying the rejection, the Office Action alleges that the claimed invention is too broad with respect to the methods for obtaining the crystals of the instant application. However, the invention makes use of relatively routine protocols in protein biochemistry, comprising, for example, expression of antibody molecules (i.e., complete antibody molecules as well as antigen-binding regions thereof) and crystallizing such molecules using the methods disclosed in the present application. See, for example, paragraphs [0046] to [0055] of the published US application (US patent app. pub. No. 2007-0122411) and the disclosure contained in Examples.

The amount of direction or guidance present

The Office Action at page 4 alleges that the specification only teaches precipitation of 20 μg/ml Erbitux™ in 10 mM phosphate buffer pH 8.0 or 10 mM citrate buffer pH 5.5 and further adding saturated ammonium sulfate in 10 mM phosphate buffer pH 8.0 or 50% (v/v) ethanol in 10 mM citrate buffer pH 5.5 and shaking the resultant mixture at 4°C to precipitate the antibody crystals. This contention is misplaced. For example, the disclosure in Example 5 of the specification explicitly teaches the use of polyethylene glycol (PEG) as a precipitation reagent.

Moreover, in Example 7, the specification further teaches that "the precipitates obtained in Examples 4 and 5 were re-dispersed and investigated by FT-IR spectrometry [wherein it was found that] the amide I-2 derivation spectra of the starting material before precipitation and of the redispersed precipitate were congruent." As such, contrary to the PTO's contentions, the specification provides further details on the use of PEG as a precipitation reagent.

The Office Action further proceeds to allege that "there is considerably [sic] unpredictability in crystallizing any protein or antibody...because the smallest change in any parameter in crystallizing protein or antibody can have enormous consequences." The Office Action cites references by Weber et al. ("Overview of Protein Crystallization Methods." *Methods in Enzymology*, 1997), MacPherson et al. (*European Journal of Biochemistry*, 1990), Kundrot et al. (*Cell Mol. Life Sci.*, 2004), Benevnuti et al. (*Nature Protocols*, 2007), Kudney et al. ("Protein Crystallization and Dumb Luck." *Principles of Protein X-ray Crystallography*, 1999) and Ahamed (*Biochemical Journal*, 2007) to support this contention. These allegations are respectfully traversed. Furthermore, provided herewith is a detailed analysis of the references that were utilized by the PTO to support the holding of non-enablement.

(1) Weber et al. (1997)

Weber (published in 1997) is fully six years before the earliest priority date of the instant application (i.e., November 29, 2003), and as such, fails to appreciate the progress made in the field of X-ray crystallography during this period. Contrary to the PTO's contention, Applicants submit that Weber, although directed to protein crystallization, supports Applicants' assertion of enablement, for example, with respect to conditions employed in protein precipitation and subsequent crystallization. Favorable consideration is respectfully requested.

(2) MacPherson et al.

MacPherson, which is published thirteen years prior to Applicants earliest priority date, further provides an overview of challenges associated with crystallization of large macromolecules, including, viruses, polynucleotides, and the like. Although not much specific guidance as to crystallization of antibody molecules, in Fig. 6, the reference teaches that crystals of albumin (a globular protein of 67 kDa, which is structurally similar to an antibody) can be obtained.

(3) Kundrot et al.

Kundrot relates to methods for obtaining crystals of proteins. Holen explicitly states that protein crystallization involves (a) target preparation, (b) screening, and (c) optimization. Each of the aforementioned aspects is further described in detail. The disclosure in Kundrot reflects the routineness in the crystallization of proteins. The described experiments are feasible without undue experimentation. Given the types of precipitation reagents disclosed herein, the total number of experiments represents a very finite number of tests that are required to arrive at the specific conditions for crystallization of antibodies. Further in their conclusion the authors only speculate on the possibly rare nature of some complex proteins, e.g., due to conformational heterogeneity and/or formation of complexes. There is no mention of relatively simple protein molecules such as antibodies or single-chain fragments thereof which bind to an antigen of interest. In contrast thereto, Applicants' specification provides explicit disclosure that the target monoclonal antibody can be crystallized. Therefore, in accordance with Kundrot et al., the claimed antibodies can be routinely crystallized without undue experimentation.

(4) Benevenuti et al. (*Nature Protocols*, 2007)

The post-published disclosure by Benevenuti provides a detailed protocol for "optimization" of protein crystallization. It is taught that protein crystallization can be routinely conducted by using a block strategy involving (a) preliminary sample preparation, (b) solubility screening, (c) fast screening of crystallization conditions to find ranges of variables (e.g., protein concentration, precipitant, pH and temperature), (d) optimization of crystallization and (e) optimization of screening. It is further taught that mutagenesis experiments and NMR analysis can further aid the understanding of the crystal structure of unfolded or mobile domains. Benevenuti explicitly teaches that using the aforementioned

approach, "even largely unstructured proteins can be crystallized." This demonstrates routineness of approach.

(5) Kudney et al.

Kudney et al. generically teaches that it is difficult to predict conditions for growing protein crystals, but fails to provide any specific guidance on the crystallization of globular (i.e., water-soluble) proteins, such as antibody molecules. It is art appreciated, for example, that transmembrane (i.e., integral) proteins are more difficult to crystallize than globular proteins (due to, for example, difficulties in expression, difficulties in solubilization, and difficulties in crystallization).

(6) Ahamed et al. (2007)

Ahamed is the **sole** publication among those cited by the Examiner that is directed to crystallization of antibodies. All the aforementioned publications are generically directed to crystallization of proteins, more specifically, large macromolecular complexes. Ahamed generically teaches that successful crystallization of antibodies has been reported in literature but the crystallization of IDEC-152 MAb (Biogen-Idec, San Diego, CA) has been particularly challenging. It should be noted that IDEC-152 MAb is a heavily glycosylated protein that is different from the MAb c225 of the instant application. For a general disclosure on antibody crystallization techniques, the Examiner is requested to refer to the cited publications, e.g., Harris et al. ("Crystallographic structure of an intact IgG1 monoclonal antibody." J. Mol. Biol. 275:861-872, 1998), Larson et al. ("Characterization of crystals of an intact monoclonal antibody from canine lymphoma." J. Mol. Biol. 222:17-19, 1992), Stura et al. ("Crystallization of an intact monoclonal antibody (4B7) against Plasmodium falciparum malaria with peptides from the Pfs25 protein antigen." Acta Crystallogr., D50:556-562, 1994), Harris et al. ("Crystallization of intact monoclonal antibodies." Proteins, 23:285-289, 1995), Kuznetsov et al. ("The liquid protein phase in crystallization: a case study-intact immunoglobulins." J. Cryst. Growth. 232:30-39, 2001) and Saphire et al. ("Crystallization and primary structure determination of an intact human immunoglobulin, b12: an antibody that broadly neutralizes primary isolates of HIV-1." Acta Crystallogr. D57:168-171, 2001).

As to the representative IDEC-152 MAb, Ahamed states that the antibody could not be crystallized with commercial kits, and thus a study of its phase behavior with respect to B22 values was carried out for a better understanding of the parameters involved in

crystallization. Ahamed further provides phase diagrams of IDEC-152 as a function of different classes of precipitants, provides measurement of B22 values by SIC, which are then correlated with the phase diagrams. Subsequently, a single MAb phase diagram displaying solubility, B22, and the optimal crystallization region is mapped. This phase diagram is useful not only in developing a fundamental understanding of the phase behavior of MAbs, but also in understanding the reason why certain proteins are extremely difficult to crystallize. See the concluding paragraph of the INTRODUCTION section. A modeling equation for protein phase diagram is further presented, which is then used to predict the phase behavior of the monoclonal antibody. See Figs. 6–8 of Ahamed et al. This favors Applicants' position that the claimed cetuximab monoclonal antibody, which is different from the IDEC-152 MAb of Ahamed, can be crystallized using routine crystallization conditions.

Applicants submit that in the absence of further evidence, the claims must be taken to satisfy the requirements of 35 U.S.C. §112, first paragraph (*In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971)). In light of the detailed disclosure in Applicants' specification, to assert a lack of enablement, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Patent Office has not presented any specific evidence to refute the findings or the conclusions made in the specification or the supporting publications. In addition, no evidence has been presented to support the contention that the claimed chimeric monoclonal antibody molecules could not be generated, in a manner that is commensurate with Applicants' claimed invention. Only unsupported allegations and conclusions regarding the "complexity" and "unpredictability" of the "state of the art" are provided to support the contention. These allegations are especially weak in the face of the showing that crystallization conditions are well-described in Applicants' own specification. Furthermore, given the rapid technological progress made in the field of protein x-ray crystallography, a skilled artisan could utilize the techniques disclosed in Applicants' own specification (Examples 1–8) for *identification* of other routine parameters for screening and optimization of crystallization conditions. This process would constitute nothing more than routine work to those in the art. As clearly established in *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998):

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. (Emphasis added)

Thus, based on routine nature of biochemical assays and the disclosure provided by Applicants' own specification and the art knowledge of antibody crystallization, it is hereby submitted that the subject matter of Applicants' claims are fully enabled.

Unpredictability and state of the art

In view of the amendments presented herein, it is respectfully submitted that the allegations on the unpredictability due to alleged complexity of antibody molecules are respectfully traversed.

The allegations of unpredictability are partly based on the teachings of aforementioned references. Applicants respectfully submit that the tools/methodology involved in such tests constituted nothing beyond what is routine in the art. For example, given the extent of the disclosure provided in Applicants' specification, it would have, at most, involved routine experimentation, if any at all, for one skilled in the art to utilize the method(s) of the instant invention for the crystallization of the c225 antibody molecule. Even absent the disclosure as discussed above, the rejection is not supported under general controlling case law. The courts have placed a burden on the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. See example *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Working examples

There is no requirement that Applicant provide any working examples relating to the treatment of the diseases to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-503, 190 USPQ 214 (CCPA 1976).See, for example, *In re Howarth*, 654 F.2d 105, 210 USPQ 689 (CCPA 1981); and *In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA 1962). However, from the Examples provided in the instant invention it is clear that the specification provides clear guidance on how to employ precipitation reagents to arrive at the claimed crystals of the chimeric monoclonal antibody molecules.

In contrast, the present Office Action has not presented any evidence to refute the findings described in Applicants' specification; nor has the Office Action established any scientific credibility to support the contention that the claimed method(s) could not be used. To this end, Ahamed's assertion that "the crystallization of proteins in (NH4)2SO4 (at pH 7.6) is rather difficult, because both solubility and B22 decrease drastically above a certain (NH4)2SO4 concentration [thus] leaving an extremely narrow window of crystallization" does not negate the findings made in the instant application, i.e., MAb c225 can be precipitated

and crystallized in a solution of ammonium phosphate at pH 8.0. A lack of predictability, for example, due to pH parameters, can be addressed by routine experimentation which is permissible under the statute. A considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to direction which the experimentation should proceed. See, *In re Wands* cited by the Examiner). Moreover, as stated in *In re Brana*, 51 F.3d 1516, 34 USPQ 1436 (Fed. Cir. 1995), an Applicant is not required to test each and every embodiment of the claimed invention. The same rationale applies to meeting the enablement and disclosure requirements of 35 U.S.C. §112, ¶1. The specification provides more than it needs, for example, precipitation reagents and conditions for crystallization of c225. In similar fashion, a skilled biochemist, by performing the same or similar tests, can determine whether such assays can be used in the treatment of complications beyond those that are exemplified in the present Examples.

Quantity of required experimentation

As can be seen from the forgoing, only routine experimentation would be needed to carry out any embodiment within the scope of the claims.

Supporting publications

Abstracts of the supporting publications by Harris et al. (J. Mol. Biol. 275:861-872, 1998), Harris et al. "The three-dimensional structure of an intact monoclonal antibody for canine lymphoma" *Nature*, 360(6402):369-72, 1992), Larson et al. (J. Mol. Biol. 222:17-19, 1991), Stura et al. (Acta Crystallogr., D50:556-562, 1994), Harris et al. (Proteins, 23:285-289, 1995), Kuznetsov et al. (J. Cryst. Growth. 232:30-39, 2001) and Saphire et al. (Acta Crystallogr. D57:168-171, 2001) are enclosed herewith for the Examiner's review. Each of the publications describes methods and reagents employed in crystallization of intact antibody molecules.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine within the art. The statute requires nothing more. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

Reg. No. L0510
For Applicant(s)

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-3169

Date: January 5, 2011